in which the NF-κB-dependent ETS transcription factor, Elf3, is either knocked out specifically in cartilage (Col2a1Cre;Elf3fl/fl) or overexpressed in cartilage and synovium (ComptTA;TRE-Elf3) to analyze the impact on OA initiation and progression. In this session, I will address the in vitro and in vitro models that we use in our research to understand how these mediators play pivotal roles in OA disease by coordinating a complex, multilayered signaling network.

I-7
PLACEBO RESPONSE: IT'S ROLE IN OA RESEARCH AND CLINICAL PRACTICE

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Purpose: To review recent research on placebo and nocebo of relevance to osteoarthritis.
Methods: Literature reviews, psycho-physiological experiments, recordings of patient-practitioner interactions, and qualitative interviews with people with pain and osteoarthritis.
Results: The placebo response is a purely artificial phenomenon: it is the response seen to an inert, sham or dummy therapy administered as a comparator to a tested intervention in the unreal, experimental context of a clinical trial. It is poorly understood, and sometimes considered a 'nuisance' to trialists and those at the forefront of the evidence based medicine movement. But it provides us with insights into one of the most important phenomena in clinical medicine: the ability of people to get symptomatically better without the use of any specific intervention.
In trials of interventions designed to help people with osteoarthritis (OA) we see large placebo responses, particularly for symptoms such as pain and stiffness. In a systematic review/meta-analysis, the effect size of placebos for OA symptoms was found to be around 0.5, which is greater than that of many accepted interventions used. Injections have a greater placebo effect than tablets, and trials using sham surgery have shown that several surgical procedures used for people with OA, such as arthroscopic washouts of the knee, are not superior to the sham intervention. Clearly, a better understanding of what factors are involved in producing a large placebo effect would help people trying to assess new interventions for OA.
The placebo effect is seen in response to many different types of intervention, and the symptoms (but probably not the pathology) of many different diseases can respond to placebos used in clinical trials. Some of the best research has come from work on models of acute pain, on Parkinson's disease and depression, and these disorders may be better models than OA for the exploration of the psychological and neurological mechanisms involved. Early research on mechanisms concentrated on psychological factors: expectations and conditioning were considered the key mechanisms, with other factors such as anxiety (which can reduce the response) also involved. More recently functional neuro-imaging and neurophysiological studies have come to dominate the literature. It would seem that placebo analgesia may involve activation of the descending inhibitory pathways of pain control, and be mediated, in part, by intrinsic opiods; however, there is clearly heterogeneity within mechanisms as well as the clinical responses. Other neurological theories have been postulated, including activation of the polyvagal system and functional connectivity.
Clinicians trying to help people with OA need to consider all aspects of the context in which they deliver care to people with OA, in order to maximise the benefit that can accrue from the non-specific (placebo) aspects of their interventions. We have self-healing potential, and what we discuss as a 'placebo effect' is a part of the even bigger, more important phenomenon of activated self-healing of body mind and spirit.
Attention has recently been re-drawn to the power of the placebo's 'evil twin' - the nocebo effect. It is clear that negative expectations and anxiety can result in pain getting worse instead of better, and a recent research report entitled 'bad is more powerful than good' cites the psychological evidence that suggests that we are more susceptible to negative influences on our bodies and minds than to positive ones.
Conclusions: Context (placebo) effects are a major component of the symptomatic response of people with OA to conventional interventions. However, many patient-practitioner interactions inadvertently result in the opposite effect (a nocebo response). We need to learn how to use the former to the advantage of our patients, and avoid the latter.

I-8
ENDOGENOUS MECHANISMS AND PATHWAYS OF CARTILAGE HEALING

F. Beier. *Western Univ., London, ON, Canada*

Cartilage degeneration is the major hallmark of osteoarthritis. The repair and renewal capacity of articular cartilage has long been thought to be extremely limited. However, recent evidence for endogenous cartilage repair has cast doubt on this dogma. I will review recent literature on this process, the molecular mechanisms involved, and potential factors influencing renewal capacity (age, genetic background etc.). I will also focus on the pathways regulating development of articular cartilage, with the underlying working model that manipulation of these pathways is a promising strategy to promote growth and repair of articular cartilage. In this context I will present our recent data showing that cartilage-specific inactivation of the signaling molecule Mig-6 in mice results in marked increases in articular cartilage thickness and articular chondrocyte proliferation.

I-9
CLINICAL DEFINITIONS OF EARLY OA: IMPLICATIONS FOR PREVENTION

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Advances in imaging and other biomarkers have been actively extending knowledge on molecular and pre-radiographic stages of osteoarthritis pathology. However, the interpretation of biomarkers typically demands knowledge of their relationship to clinically important states or events, either at the time of biomarker acquisition or in the future. Therefore within this expanding view of the natural history of osteoarthritis lies a set of complex challenges. Among these challenges are (i) to reflect on how and at what stage in the natural history of the condition patients currently present to health services; (ii) to elucidate the nature and timing of emergent signs and symptoms in relation to biomarker-defined disease states and their significance for future clinically important states and events.
Currently, if detection of OA is assumed to be the point of recorded clinical diagnosis of OA in routine primary care, electronic health record (EHR) database studies suggest that this occurs relatively late in the pathological process, and varies substantially between individual practitioners. This does not, however, fully capture when symptomatic osteoarthritis first presents nor when management begins. An unclear proportion of osteoarthritis diagnoses are preceded by prior consultations for joint symptoms labelled as non-specific problems. However, the longitudinal pattern of these prior consultations together with other risk factor information held within the EHR may be exploited for risk prediction algorithms. Qualitative studies of the osteoarthritis consultation in primary care provide additional examples of symptoms of OA presented as mere 'fragments' in the doctor-patient interaction or as 'door handle' problems that remain off the record but which in theory present opportunities for earlier recognition and management of OA. A critical issue is which of these presenting signs and symptoms are of real prognostic significance.
Findings from a series of population-based prospective observational cohort studies provide evidence on several symptoms and signs occurring in a pre-radiographic stage that can precede, and are associated with an increased risk of, the incidence of frank structural abnormality on plain radiographs. In recent analyses a possible prodromal phase of increasing likelihood of symptoms among cases developing incident radiographic OA has been described. However, the ability of these early signs and symptoms to consistently identify individuals with a high absolute risk of future clinically important states and events cannot be assumed. A single irreversible transition into progressive OA may not be the norm and extended periods of apparent non-progressive symptoms and functional limitation have been reported. Furthermore, it remains possible that the majority of cases of progressive or ultimately severely disabling cases arise not from the few individuals classed as high risk but from the many classed as low-medium risk (Rose's prevention paradox).